D1

SEQUENCE LISTING

<110> WALLACH, David
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KOVALENKO, Andrei
VARFOLOMEEV, Eugene
BRODIANSKI, Vadim

<120> CASH (CASPASE HOMOLOGUE) WITH DEATH EFFECTOR DOMAIN, MODULATORS OF THE FUNCTION OF FAS RECEPTORS

<130> WALLACH=23

<140> 09/380,546
<141> 1999-11-29

<150> PCT/IL98/00098
<151> 1998-02-26

<150> IL 120367
<151> 1997-03-03

<150> IL120759
<151> 1997-05-01

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<170> PatentIn Ver. 2.0

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cacagtgagt gccggctatt ggacttttgt ccagtgacag ctgagacaac aaggaccacg 180

ggaggaggtg taggagagaa gcgccgcgaa cagcgatcgc ccagcaccaa gtccgcttcc 240

aggctttcgg tttctttgcc tccatcttgg gtgcgccttc ccggcgtcta ggggagcgaa 300

ggctgaggtg gcagcggcag gagagtccgg ccgcgacagg acgaactccc ccactggaaa 360

ggattctgaa agaaatgaag tcagccctca gaaatgaagt tgactgcctg ctggctttcc 420

tgttgactgg cccggagctg tactgcaaga cccttgtgag cttccctagt ctaagagtag 480

g atg tct gct gaa gtc atc cat cag gtt gaa gaa gca ctt gat aca gat 529
Met Ser Ala Glu Val Ile His Gln Val Glu Glu Ala Leu Asp Thr Asp
1 5 10 15

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gag aag gag atg ctg ctc ttt ttg tgc cgg gat gtt gct ata gat gtg   577
Glu Lys Glu Met Leu Leu Phe Leu Cys Arg Asp Val Ala Ile Asp Val
            20                  25                  30

gtt cca cct aat gtc agg gac ctt ctg gat att tta cgg gaa aga ggt   625
Val Pro Pro Asn Val Arg Asp Leu Leu Asp Ile Leu Arg Glu Arg Gly
         35                  40                  45

aag ctg tct gtc ggg gac ttg gct gaa ctg ctc tac aga gtg agg cga   673
Lys Leu Ser Val Gly Asp Leu Ala Glu Leu Leu Tyr Arg Val Arg Arg
     50                  55                  60

ttt gac ctg ctc aaa cgt atc ttg aag atg gac aga aaa gct gtg gag   721
Phe Asp Leu Leu Lys Arg Ile Leu Lys Met Asp Arg Lys Ala Val Glu
 65                  70                  75                  80

acc cac ctg ctc agg aac cct cac ctt gtt tcg gac tat aga gtg ctg   769
Thr His Leu Leu Arg Asn Pro His Leu Val Ser Asp Tyr Arg Val Leu
                85                  90                  95

atg gca gag att ggt gag gat ttg gat aaa tct gat gtg tcc tca tta   817
Met Ala Glu Ile Gly Glu Asp Leu Asp Lys Ser Asp Val Ser Ser Leu
            100                 105                 110

att ttc ctc atg aag gat tac atg ggc cga ggc aag ata agc aag gag   865
Ile Phe Leu Met Lys Asp Tyr Met Gly Arg Gly Lys Ile Ser Lys Glu
        115                 120                 125

aag agt ttc ttg gac ctt gtg gtt gag ttg gag aaa cta aat ttg gtt   913
Lys Ser Phe Leu Asp Leu Val Val Glu Leu Glu Lys Leu Asn Leu Val
    130                 135                 140

gcc cca gat caa ctg gat tta tta gaa aaa tgc cta aag aac atc cac   961
Ala Pro Asp Gln Leu Asp Leu Leu Glu Lys Cys Leu Lys Asn Ile His
145                 150                 155                 160

aga ata gac ctg aag aca aaa atc cag aag tac aag cag tct gtt caa   1009
Arg Ile Asp Leu Lys Thr Lys Ile Gln Lys Tyr Lys Gln Ser Val Gln
                165                 170                 175

gga gca ggg aca agt tac agg aat gtt ctc caa gca gca atc caa aag   1057
Gly Ala Gly Thr Ser Tyr Arg Asn Val Leu Gln Ala Ala Ile Gln Lys
            180                 185                 190

agt ctc aag gat cct tca aat aac ttc agg ctc cat aat ggg aga agt   1105
Ser Leu Lys Asp Pro Ser Asn Asn Phe Arg Leu His Asn Gly Arg Ser
        195                 200                 205

aaa gaa caa aga ctt aag gaa cag ctt ggc gct caa caa gaa cca gtg   1153
Lys Glu Gln Arg Leu Lys Glu Gln Leu Gly Ala Gln Gln Glu Pro Val
    210                 215                 220

aag aaa tcc att cag gaa tca gaa gct ttt ttg cct cag agc ata cct   1201
Lys Lys Ser Ile Gln Glu Ser Glu Ala Phe Leu Pro Gln Ser Ile Pro
225                 230                 235                 240
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gaa gag aga tac aag atg aag agc aag ccc cta gga atc tgc ctg ata   1249
Glu Glu Arg Tyr Lys Met Lys Ser Lys Pro Leu Gly Ile Cys Leu Ile
                245                 250                 255

atc gat tgc att ggc aat gag aca gag ctt ctt cga gac acc ttc act   1297
Ile Asp Cys Ile Gly Asn Glu Thr Glu Leu Leu Arg Asp Thr Phe Thr
            260                 265                 270

tcc ctg ggc tat gaa gtc cag aaa ttc ttg cat ctc agt atg cat ggt   1345
Ser Leu Gly Tyr Glu Val Gln Lys Phe Leu His Leu Ser Met His Gly
        275                 280                 285

ata tcc cag att ctt ggc caa ttt gcc tgt atg ccc gag cac cga gac   1393
Ile Ser Gln Ile Leu Gly Gln Phe Ala Cys Met Pro Glu His Arg Asp
    290                 295                 300

tac gac agc ttt gtg tgt gtc ctg gtg agc cga gga ggc tcc cag agt   1441
Tyr Asp Ser Phe Val Cys Val Leu Val Ser Arg Gly Gly Ser Gln Ser
305                 310                 315                 320

gtg tat ggt gtg gat cag act cac tca ggg ctc ccc ctg cat cac atc   1489
Val Tyr Gly Val Asp Gln Thr His Ser Gly Leu Pro Leu His His Ile
                325                 330                 335

agg agg atg ttc atg gga gat tca tgc cct tat cta gca ggg aag cca   1537
Arg Arg Met Phe Met Gly Asp Ser Cys Pro Tyr Leu Ala Gly Lys Pro
            340                 345                 350

aag atg ttt ttt att cag aac tat gtg gtg tca gag ggc cag ctg gag   1585
Lys Met Phe Phe Ile Gln Asn Tyr Val Val Ser Glu Gly Gln Leu Glu
        355                 360                 365

aac agc agc ctc ttg gag gtg gat ggg cca gcg atg aag aat gtg gaa   1633
Asn Ser Ser Leu Leu Glu Val Asp Gly Pro Ala Met Lys Asn Val Glu
    370                 375                 380

ttc aag gct cag aag cga ggg ctg tgc aca gtt cac cga gaa gct gac   1681
Phe Lys Ala Gln Lys Arg Gly Leu Cys Thr Val His Arg Glu Ala Asp
385                 390                 395                 400

ttc ttc tgg agc ctg tgt act gcg gac atg tcc ctg ctg gag cag tct   1729
Phe Phe Trp Ser Leu Cys Thr Ala Asp Met Ser Leu Leu Glu Gln Ser
                405                 410                 415

cac agc tca ccg tcc ctg tac ctg cag tgc ctc tcc cag aaa ctg aga   1777
His Ser Ser Pro Ser Leu Tyr Leu Gln Cys Leu Ser Gln Lys Leu Arg
            420                 425                 430

caa gaa aga aaa cgc cca ctc ctg gat ctt cac att gaa ctc aat ggc   1825
Gln Glu Arg Lys Arg Pro Leu Leu Asp Leu His Ile Glu Leu Asn Gly
        435                 440                 445

tac atg tat gat tgg aac agc aga gtt tct gcc aag gag aaa tat tat   1873
Tyr Met Tyr Asp Trp Asn Ser Arg Val Ser Ala Lys Glu Lys Tyr Tyr
    450                 455                 460
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gtc tgg ctg cag cac act ctg aga aag aaa ctt atc ctc tcc tac aca   1921
Val Trp Leu Gln His Thr Leu Arg Lys Lys Leu Ile Leu Ser Tyr Thr
465                 470                 475                 480

taagaaacca aaaggctggg cgtagtggct cacacctgta atcccagcac tttgggaggc 1981

caaggagggc agatcacttc aggtcaggag ttcgagacca gcctggccaa catggtaaac 2041

gctgtcccta gtaaaaatgc aaaaattagc tgggtgtggg tgtgggtacc tgtgttccca 2101

gttacttggg aggctgaggt gggaggatct tttgaaccca ggagttcagg gtcatagcat 2161

gctgtgattg tgcctacgaa tagccactgc ataccaacct gggcaatata gcaagatccc 2221

atctctttaa aaaaaaaaaa aa                                          2243
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<213> Homo sapiens

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Glu Lys Glu Met Leu Leu Phe Leu Cys Arg Asp Val Ala Ile Asp Val
             20                  25                  30

Val Pro Pro Asn Val Arg Asp Leu Leu Asp Ile Leu Arg Glu Arg Gly
         35                  40                  45

Lys Leu Ser Val Gly Asp Leu Ala Glu Leu Leu Tyr Arg Val Arg Arg
     50                  55                  60

Phe Asp Leu Leu Lys Arg Ile Leu Lys Met Asp Arg Lys Ala Val Glu
 65                  70                  75                  80

Thr His Leu Leu Arg Asn Pro His Leu Val Ser Asp Tyr Arg Val Leu
                 85                  90                  95

Met Ala Glu Ile Gly Glu Asp Leu Asp Lys Ser Asp Val Ser Ser Leu
            100                 105                 110

Ile Phe Leu Met Lys Asp Tyr Met Gly Arg Gly Lys Ile Ser Lys Glu
        115                 120                 125

Lys Ser Phe Leu Asp Leu Val Val Glu Leu Glu Lys Leu Asn Leu Val
    130                 135                 140

Ala Pro Asp Gln Leu Asp Leu Leu Glu Lys Cys Leu Lys Asn Ile His
145                 150                 155                 160

Arg Ile Asp Leu Lys Thr Lys Ile Gln Lys Tyr Lys Gln Ser Val Gln
                165                 170                 175

Gly Ala Gly Thr Ser Tyr Arg Asn Val Leu Gln Ala Ala Ile Gln Lys
            180                 185                 190
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Ser Leu Lys Asp Pro Ser Asn Asn Phe Arg Leu His Asn Gly Arg Ser
        195                 200                 205

Lys Glu Gln Arg Leu Lys Glu Gln Leu Gly Ala Gln Gln Glu Pro Val
    210                 215                 220

Lys Lys Ser Ile Gln Glu Ser Glu Ala Phe Leu Pro Gln Ser Ile Pro
225                 230                 235                 240

Glu Glu Arg Tyr Lys Met Lys Ser Lys Pro Leu Gly Ile Cys Leu Ile
                245                 250                 255

Ile Asp Cys Ile Gly Asn Glu Thr Glu Leu Leu Arg Asp Thr Phe Thr
            260                 265                 270

Ser Leu Gly Tyr Glu Val Gln Lys Phe Leu His Leu Ser Met His Gly
        275                 280                 285

Ile Ser Gln Ile Leu Gly Gln Phe Ala Cys Met Pro Glu His Arg Asp
    290                 295                 300

Tyr Asp Ser Phe Val Cys Val Leu Val Ser Arg Gly Gly Ser Gln Ser
305                 310                 315                 320

Val Tyr Gly Val Asp Gln Thr His Ser Gly Leu Pro Leu His His Ile
                325                 330                 335

Arg Arg Met Phe Met Gly Asp Ser Cys Pro Tyr Leu Ala Gly Lys Pro
            340                 345                 350

Lys Met Phe Phe Ile Gln Asn Tyr Val Val Ser Glu Gly Gln Leu Glu
        355                 360                 365

Asn Ser Ser Leu Leu Glu Val Asp Gly Pro Ala Met Lys Asn Val Glu
    370                 375                 380

Phe Lys Ala Gln Lys Arg Gly Leu Cys Thr Val His Arg Glu Ala Asp
385                 390                 395                 400

Phe Phe Trp Ser Leu Cys Thr Ala Asp Met Ser Leu Leu Glu Gln Ser
                405                 410                 415

His Ser Ser Pro Ser Leu Tyr Leu Gln Cys Leu Ser Gln Lys Leu Arg
            420                 425                 430

Gln Glu Arg Lys Arg Pro Leu Leu Asp Leu His Ile Glu Leu Asn Gly
        435                 440                 445

Tyr Met Tyr Asp Trp Asn Ser Arg Val Ser Ala Lys Glu Lys Tyr Tyr
    450                 455                 460

Val Trp Leu Gln His Thr Leu Arg Lys Lys Leu Ile Leu Ser Tyr Thr
465                 470                 475                 480
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cacagtgagt gccggctatt ggacttttgt ccagtgacag ctgagacaac aaggaccacg 180

ggaggaggtg taggagagaa gcgccgcgaa cagcgatcgc ccagcaccaa gtccgcttcc 240

aggctttcgg tttctttgcc tccatcttgg gtgcgccttc ccggcgtcta ggggagcgaa 300

ggctgaggtg gcagcggcag gagagtccgg ccgcgacagg acgaactccc ccactggaaa 360

ggattctgaa agaaatgaag tcagccctca gaaatgaagt tgactgcctg ctggctttcc 420

tgttgactgg cccggagctg tactgcaaga cccttgtgag cttccctagt ctaagagtag 480

g atg tct gct gaa gtc atc cat cag gtt gaa gaa gca ctt gat aca gat 529
  Met Ser Ala Glu Val Ile His Gln Val Glu Glu Ala Leu Asp Thr Asp
    1   5   10   15

gag aag gag atg ctg ctc ttt ttg tgc cgg gat gtt gct ata gat gtg 577
Glu Lys Glu Met Leu Leu Phe Leu Cys Arg Asp Val Ala Ile Asp Val
             20   25   30

gtt cca cct aat gtc agg gac ctt ctg gat att tta cgg gaa aga ggt 625
Val Pro Pro Asn Val Arg Asp Leu Leu Asp Ile Leu Arg Glu Arg Gly
         35   40   45

aag ctg tct gtc ggg gac ttg gct gaa ctg ctc tac aga gtg agg cga 673
Lys Leu Ser Val Gly Asp Leu Ala Glu Leu Leu Tyr Arg Val Arg Arg
     50   55   60

ttt gac ctg ctc aaa cgt atc ttg aag atg gac aga aaa gct gtg gag 721
Phe Asp Leu Leu Lys Arg Ile Leu Lys Met Asp Arg Lys Ala Val Glu
 65   70   75   80

acc cac ctg ctc agg aac cct cac ctt gtt tcg gac tat aga gtg ctg 769
Thr His Leu Leu Arg Asn Pro His Leu Val Ser Asp Tyr Arg Val Leu
                 85   90   95

atg gca gag att ggt gag gat ttg gat aaa tct gat gtg tcc tca tta 817
Met Ala Glu Ile Gly Glu Asp Leu Asp Lys Ser Asp Val Ser Ser Leu
            100   105   110

att ttc ctc atg aag gat tac atg ggc cga ggc aag ata agc aag gag 865
Ile Phe Leu Met Lys Asp Tyr Met Gly Arg Gly Lys Ile Ser Lys Glu
        115   120   125

```
aag agt ttc ttg gac ctt gtg gtt gag ttg gag aaa cta aat ttg gtt   913
Lys Ser Phe Leu Asp Leu Val Val Glu Leu Glu Lys Leu Asn Leu Val
    130                 135                 140

gcc cca gat caa ctg gat tta tta gaa aaa tgc cta aag aac atc cac   961
Ala Pro Asp Gln Leu Asp Leu Leu Glu Lys Cys Leu Lys Asn Ile His
145                 150                 155                 160

aga ata gac ctg aag aca aaa atc cag aag tac aag cag tct gtt caa   1009
Arg Ile Asp Leu Lys Thr Lys Ile Gln Lys Tyr Lys Gln Ser Val Gln
                165                 170                 175

gga gca ggg aca agt tac agg aat gtt ctc caa gca gca atc caa aag   1057
Gly Ala Gly Thr Ser Tyr Arg Asn Val Leu Gln Ala Ala Ile Gln Lys
            180                 185                 190

agt ctc aag gat cct tca aat aac ttc agg atg ata aca ccc tat gcc   1105
Ser Leu Lys Asp Pro Ser Asn Asn Phe Arg Met Ile Thr Pro Tyr Ala
        195                 200                 205

cat tgt cct gat ctg aaa att ctt gga aat tgt tcc atg tgattaacat    1154
His Cys Pro Asp Leu Lys Ile Leu Gly Asn Cys Ser Met
    210                 215                 220

ggaactgcct ctacttaatc attctgaatg attaaatcgt ttcattttct aaatgtgtta 1214

taatgtgttt agccctttct tgttgctgta tgtttagatg ctttccaatc ttttgttact 1274

actaataatg ctataaaata aatatccttg tacttcttaa aaaaaaaaaa aaaaaaaaaa 1334

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaa                        1373
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Glu Lys Glu Met Leu Leu Phe Leu Cys Arg Asp Val Ala Ile Asp Val
             20                  25                  30

Val Pro Pro Asn Val Arg Asp Leu Leu Asp Ile Leu Arg Glu Arg Gly
         35                  40                  45

Lys Leu Ser Val Gly Asp Leu Ala Glu Leu Leu Tyr Arg Val Arg Arg
     50                  55                  60

Phe Asp Leu Leu Lys Arg Ile Leu Lys Met Asp Arg Lys Ala Val Glu
 65                  70                  75                  80

Thr His Leu Leu Arg Asn Pro His Leu Val Ser Asp Tyr Arg Val Leu
                 85                  90                  95
```

```
Met Ala Glu Ile Gly Glu Asp Leu Asp Lys Ser Asp Val Ser Ser Leu
            100                 105                 110

Ile Phe Leu Met Lys Asp Tyr Met Gly Arg Gly Lys Ile Ser Lys Glu
        115                 120                 125

Lys Ser Phe Leu Asp Leu Val Val Glu Leu Glu Lys Leu Asn Leu Val
    130                 135                 140

Ala Pro Asp Gln Leu Asp Leu Leu Glu Lys Cys Leu Lys Asn Ile His
145                 150                 155                 160

Arg Ile Asp Leu Lys Thr Lys Ile Gln Lys Tyr Lys Gln Ser Val Gln
                165                 170                 175

Gly Ala Gly Thr Ser Tyr Arg Asn Val Leu Gln Ala Ala Ile Gln Lys
            180                 185                 190

Ser Leu Lys Asp Pro Ser Asn Asn Phe Arg Met Ile Thr Pro Tyr Ala
        195                 200                 205

His Cys Pro Asp Leu Lys Ile Leu Gly Asn Cys Ser Met
    210                 215                 220
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<213> Mus musculus

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Cys Leu Asp Glu Asp Glu Lys Glu Met Met Leu Phe Leu Cys Arg Asp
             20                  25                  30

Val Thr Glu Asn Leu Ala Ala Pro Asn Val Arg Asp Leu Leu Asp Ser
         35                  40                  45

Leu Ser Glu Arg Gly Gln Leu Ser Phe Ala Thr Leu Ala Glu Leu Leu
     50                  55                  60

Tyr Arg Val Arg Arg Phe Asp Leu Leu Lys Arg Ile Leu Lys Thr Asp
 65                  70                  75                  80

Lys Ala Thr Val Glu Asp His Leu Arg Arg Asn Pro His Leu Val Ser
                 85                  90                  95

Asp Tyr Arg Val Leu Leu Met Glu Ile Gly Glu Ser Leu Asp Gln Asn
            100                 105                 110

Asp Val Ser Ser Leu Val Phe Leu Thr Arg Ile Thr Arg Asp Tyr Thr
        115                 120                 125

Gly Arg Gly Lys Ile Ala Lys Asp Lys Ser Phe Leu Asp Leu Val Ile
    130                 135                 140
```

```
Glu Leu Glu Lys Leu Asn Leu Ile Ala Ser Asp Gln Leu Asn Leu Leu
145                 150                 155                 160

Glu Lys Cys Leu Lys Asn Ile His Arg Ile Asp Leu Asn Thr Lys Ile
                165                 170                 175

Gln Lys Tyr Thr Gln Ser Ser Gln Gly Ala Arg Ser Asn Met Asn Thr
            180                 185                 190

Leu Gln Ala Ser Leu Pro Lys Leu Ser Ile Lys Tyr Asn Ser Arg Leu
        195                 200                 205

Gln Asn Gly Arg Ser Lys Glu Pro Arg Phe Val Glu Tyr Arg Asp Ser
    210                 215                 220

Gln Arg Thr Leu Val Lys Thr Ser Ile Gln Glu Ser Gly Ala Phe Leu
225                 230                 235                 240

Pro Pro His Ile Arg Glu Glu Thr Tyr Arg Met Gln Ser Lys Pro Leu
                245                 250                 255

Gly Ile Cys Leu Ile Ile Asp Cys Ile Gly Asn Asp Thr Lys Tyr Leu
            260                 265                 270

Gln Glu Thr Phe Thr Ser Leu Gly Tyr His Ile Gln Leu Phe Leu Phe
        275                 280                 285

Pro Lys Ser His Asp Ile Thr Gln Ile Val Arg Arg Tyr Ala Ser Met
    290                 295                 300

Ala Gln His Gln Asp Tyr Asp Ser Phe Ala Cys Val Leu Val Ser Leu
305                 310                 315                 320

Gly Gly Ser Gln Ser Met Met Gly Arg Asp Gln Val His Ser Gly Phe
                325                 330                 335

Ser Leu Asp His Val Lys Asn Met Phe Thr Gly Asp Thr Cys Pro Ser
            340                 345                 350

Leu Arg Gly Lys Pro Lys Leu Phe Phe Ile Gln Asn Tyr Glu Ser Leu
        355                 360                 365

Gly Ser Gln Leu Glu Asp Ser Ser Leu Glu Val Asp Gly Pro Ser Ile
    370                 375                 380

Lys Asn Val Asp Ser Lys Pro Leu Gln Pro Arg His Cys Thr Thr His
385                 390                 395                 400

Pro Glu Ala Asp Ile Phe Trp Ser Leu Cys Thr Ala Asp Val Ser His
                405                 410                 415

Leu Glu Lys Pro Ser Ser Ser Ser Ser Val Tyr Leu Gln Lys Leu Ser
            420                 425                 430

Gln Gln Leu Lys Gln Gly Arg Arg Arg Pro Leu Val Asp Leu His Val
        435                 440                 445
```

```
Glu Leu Met Asp Lys Val Tyr Ala Trp Asn Ser Gly Val Ser Ser Lys
    450                 455                 460

Glu Lys Tyr Ser Leu Ser Leu Gln His Thr Leu Arg Lys Lys Leu Ile
465                 470                 475                 480

Leu Ala Pro Thr
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<213> Homo sapiens

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Glu Asp Leu Ala Ser Leu Lys Phe Leu Ser Leu Asp Tyr Ile Pro Gln
             20                  25                  30

Arg Lys Gln Glu Pro Ile Lys Asp Ala Leu Met Leu Phe Gln Arg Leu
         35                  40                  45

Gln Glu Lys Arg Met Leu Glu Glu Ser Asn Leu Ser Phe Leu Lys Glu
     50                  55                  60

Leu Leu Phe Arg Ile Asn Arg Leu Asp Leu Leu Ile Thr Tyr Leu Asn
 65                  70                  75                  80

Thr Arg Lys Glu Glu Met Glu Arg Glu Leu Gln Thr Pro Gly Arg Ala
                 85                  90                  95

Gln Ile Ser Ala Tyr Arg Val Met Leu Tyr Gln Ile Ser Glu Glu Val
            100                 105                 110

Ser Arg Ser Glu Leu Arg Ser Phe Lys Phe Leu Leu Gln Glu Glu Ile
        115                 120                 125

Ser Lys Cys Lys Leu Asp Asp Asp Met Asn Leu Leu Asp Ile Phe Ile
    130                 135                 140

Glu Met Glu Lys Arg Val Ile Leu Gly Glu Gly Lys Leu Asp Ile Leu
145                 150                 155                 160

Lys Arg Val Cys Ala Gln Ile Asn Lys Ser Leu Leu Lys Ile Ile Asn
                165                 170                 175

Asp Tyr Glu Glu Phe Ser Lys Glu Arg Ser Ser Ser Leu Glu Gly Ser
            180                 185                 190

Pro Asp Glu Phe Ser Asn Gly Glu Glu Leu Cys Gly Val Met Thr Ile
        195                 200                 205

Ser Asp Ser Pro Arg Glu Gln Asp Ser Glu Ser Gln Thr Leu Asp Lys
    210                 215                 220
```

```
Val Tyr Gln Met Lys Ser Lys Pro Arg Gly Tyr Cys Leu Ile Ile Asn
225                 230                 235                 240

Asn His Asn Phe Ala Lys Ala Arg Glu Lys Val Pro Lys Leu His Ser
                245                 250                 255

Ile Arg Asp Arg Asn Gly Thr His Leu Asp Ala Gly Ala Leu Thr Thr
            260                 265                 270

Thr Phe Glu Glu Leu His Phe Glu Ile Lys Pro His Asp Asp Cys Thr
        275                 280                 285

Val Glu Gln Ile Tyr Glu Ile Leu Lys Ile Tyr Gln Leu Met Asp His
    290                 295                 300

Ser Asn Met Asp Cys Phe Ile Cys Cys Ile Leu Ser His Gly Asp Lys
305                 310                 315                 320

Gly Ile Ile Tyr Gly Thr Asp Gly Gln Glu Ala Pro Ile Tyr Glu Leu
                325                 330                 335

Thr Ser Gln Phe Thr Gly Leu Lys Cys Pro Ser Leu Ala Gly Lys Pro
            340                 345                 350

Lys Val Phe Phe Ile Gln Ala Cys Gln Gly Asp Asn Tyr Gln Lys Gly
        355                 360                 365

Ile Pro Val Glu Thr Asp Ser Glu Glu Gln Pro Tyr Leu Glu Met Asp
    370                 375                 380

Leu Ser Ser Pro Gln Thr Arg Tyr Ile Pro Asp Glu Ala Asp Phe Leu
385                 390                 395                 400

Leu Gly Met Ala Thr Val Asn Asn Cys Val Ser Tyr Arg Asn Pro Ala
                405                 410                 415

Glu Gly Thr Trp Tyr Ile Gln Ser Leu Cys Gln Ser Leu Arg Glu Arg
            420                 425                 430

Cys Pro Arg Gly Asp Asp Ile Leu Thr Ile Leu Thr Glu Val Asn Tyr
        435                 440                 445

Glu Val Ser Asn Lys Asp Asp Lys Lys Asn Met Gly Lys Gln Met Pro
    450                 455                 460

Gln Pro Thr Phe Thr Leu Arg Lys Lys Leu Val Phe Pro Ser Asp
465                 470                 475
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<213> Homo sapiens

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  1               5                  10                  15
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Lys Val Ser Phe Arg Glu Lys Leu Leu Ile Ile Asp Ser Asn Leu Gly
            20                  25                  30

Val Gln Asp Val Glu Asn Leu Lys Phe Leu Cys Ile Gly Leu Val Pro
        35                  40                  45

Asn Lys Lys Leu Glu Lys Ser Ser Ser Ala Ser Asp Val Phe Glu His
    50                  55                  60

Leu Leu Ala Gly Asp Leu Leu Ser Glu Glu Asp Pro Phe Phe Leu Ala
65                  70                  75                  80

Glu Leu Leu Tyr Ile Ile Arg Gln Lys Lys Leu Leu Gln His Leu Asn
                85                  90                  95

Cys Thr Lys Glu Glu Val Glu Arg Leu Leu Pro Thr Arg Gln Arg Val
            100                 105                 110

Ser Leu Phe Arg Asn Leu Leu Tyr Glu Leu Ser Glu Gly Ile Asp Ser
        115                 120                 125

Glu Asn Leu Lys Asp Met Ile Phe Leu Leu Lys Asp Ser Leu Pro Lys
    130                 135                 140

Thr Glu Met Thr Ser Leu Ser Phe Leu Ala Phe Leu Glu Lys Gln Gly
145                 150                 155                 160

Lys Ile Asp Glu Asp Asn Leu Thr Cys Leu Glu Asp Leu Cys Lys Thr
                165                 170                 175

Val Val Pro Lys Leu Leu Arg Asn Ile Glu Lys Tyr Lys Arg Glu Lys
            180                 185                 190

Ala Ile Gln Ile Val Thr Pro Pro Val Asp Lys Glu Ala Glu Ser Tyr
        195                 200                 205

Gln Gly Glu Glu Glu Leu Val Ser Gln Thr Asp Val Lys Thr Phe Leu
    210                 215                 220

Glu Ala Leu Pro Arg Ala Ala Val Tyr Arg Met Asn Arg Asn His Arg
225                 230                 235                 240

Gly Leu Cys Val Ile Val Asn Asn His Ser Phe Thr Ser Leu Lys Asp
                245                 250                 255

Arg Gln Gly Thr His Lys Asp Ala Glu Ile Leu Ser His Val Phe Gln
            260                 265                 270

Trp Leu Gly Phe Thr Val His Ile His Asn Asn Val Thr Lys Val Glu
        275                 280                 285

Met Glu Met Val Leu Gln Lys Gln Lys Cys Asn Pro Ala His Ala Asp
    290                 295                 300

Gly Asp Cys Phe Val Phe Cys Ile Leu Thr His Gly Arg Phe Gly Ala
305                 310                 315                 320
```

```
Val Tyr Ser Ser Asp Glu Ala Leu Ile Pro Ile Arg Glu Ile Met Ser
                325                 330                 335

His Phe Thr Ala Leu Gln Cys Pro Arg Leu Ala Glu Lys Pro Lys Leu
            340                 345                 350

Phe Phe Ile Gln Ala Cys Gln Gly Glu Glu Ile Gln Pro Ser Val Ser
        355                 360                 365

Ile Glu Ala Asp Ala Leu Asn Pro Glu Gln Ala Pro Thr Ser Leu Gln
    370                 375                 380

Asp Ser Ile Pro Ala Glu Ala Asp Phe Leu Leu Gly Leu Ala Thr Val
385                 390                 395                 400

Pro Gly Tyr Val Ser Phe Arg His Val Glu Glu Gly Ser Trp Tyr Ile
                405                 410                 415

Gln Ser Leu Cys Asn His Leu Lys Lys Leu Val Pro Arg His Glu Asp
            420                 425                 430

Ile Leu Ser Ile Leu Thr Ala Val Asn Asp Asp Val Ser Arg Arg Val
        435                 440                 445

Asp Lys Gln Gly Thr Lys Lys Gln Met Pro Gln Pro Ala Phe Thr Leu
    450                 455                 460

Arg Lys Lys Leu Val Phe Pro Val Pro Leu Asp Ala Leu Ser Ile
465                 470                 475
```

<210> 8
<211> 249
<212> PRT
<213> Homo sapiens

<400> 8

```
Ser Gly Ile Ser Leu Asp Asn Ser Tyr Lys Met Asp Tyr Pro Glu Met
  1               5                  10                  15

Gly Leu Cys Ile Ile Ile Asn Asn Lys Asn Phe His Lys Ser Thr Gly
            20                  25                  30

Met Thr Ser Arg Ser Gly Thr Asp Val Asp Ala Ala Asn Leu Arg Glu
        35                  40                  45

Thr Phe Arg Asn Leu Lys Tyr Glu Val Arg Asn Lys Asn Asp Leu Thr
    50                  55                  60

Arg Glu Glu Ile Val Glu Leu Met Arg Asp Val Ser Lys Glu Asp His
65                  70                  75                  80

Ser Lys Arg Ser Ser Phe Val Cys Val Leu Leu Ser His Gly Glu Glu
                85                  90                  95

Gly Ile Ile Phe Gly Thr Asn Gly Pro Val Asp Leu Lys Lys Ile Thr
            100                 105                 110
```

```
Asn Phe Phe Arg Gly Asp Arg Cys Arg Ser Leu Thr Gly Lys Pro Lys
        115                 120                 125

Leu Phe Ile Ile Gln Ala Cys Arg Gly Thr Glu Leu Asp Cys Gly Ile
    130                 135                 140

Glu Thr Asp Ser Gly Val Asp Asp Asp Met Ala Cys His Lys Ile Pro
145                 150                 155                 160

Val Asp Ala Asp Phe Leu Tyr Ala Tyr Ser Thr Ala Pro Gly Tyr Tyr
                165                 170                 175

Ser Trp Arg Asn Ser Lys Asp Gly Ser Trp Phe Ile Gln Ser Leu Cys
            180                 185                 190

Ala Met Leu Lys Gln Tyr Ala Asp Lys Leu Glu Phe Met His Ile Leu
        195                 200                 205

Thr Arg Val Asn Arg Lys Val Ala Thr Glu Phe Glu Ser Phe Ser Phe
    210                 215                 220

Asp Ala Thr Phe His Ala Lys Lys Gln Ile Pro Cys Ile Val Ser Met
225                 230                 235                 240

Leu Thr Lys Glu Leu Tyr Phe Tyr His
                245
```

<210> 9
<211> 300
<212> PRT
<213> Homo sapiens

<400> 9

```
Gln Gly Val Leu Ser Ser Phe Pro Ala Pro Gln Ala Val Gln Asp Asn
  1               5                  10                  15

Pro Ala Met Pro Thr Ser Ser Gly Ser Glu Gly Asn Val Lys Leu Cys
            20                  25                  30

Ser Leu Glu Glu Ala Gln Arg Ile Trp Lys Gln Lys Ser Ala Glu Ile
        35                  40                  45

Tyr Pro Ile Met Asp Lys Ser Ser Arg Thr Arg Leu Ala Leu Ile Ile
    50                  55                  60

Cys Asn Glu Glu Phe Asp Ser Ile Pro Arg Arg Thr Gly Ala Glu Val
65                  70                  75                  80

Asp Ile Thr Gly Met Thr Met Leu Leu Gln Asn Leu Gly Tyr Ser Val
                85                  90                  95

Asp Val Lys Lys Asn Leu Thr Ala Ser Asp Met Thr Thr Glu Leu Glu
            100                 105                 110

Ala Phe Ala His Arg Pro Glu His Lys Thr Ser Asp Ser Thr Phe Leu
        115                 120                 125
```

```
Val Phe Met Ser His Gly Ile Arg Glu Gly Ile Cys Gly Lys Lys His
    130                 135                 140

Ser Glu Gln Val Pro Asp Ile Leu Gln Leu Asn Ala Ile Phe Asn Met
145                 150                 155                 160

Leu Asn Thr Lys Asn Cys Pro Ser Leu Lys Asp Lys Pro Lys Val Ile
                165                 170                 175

Ile Ile Gln Ala Cys Arg Gly Asp Ser Pro Gly Val Val Trp Phe Lys
            180                 185                 190

Asp Ser Val Gly Val Ser Gly Asn Leu Ser Leu Pro Thr Thr Glu Glu
        195                 200                 205

Phe Glu Asp Asp Ala Ile Lys Lys Ala His Ile Glu Lys Asp Phe Ile
    210                 215                 220

Ala Phe Cys Ser Ser Thr Pro Asp Asn Val Ser Trp Arg His Pro Thr
225                 230                 235                 240

Met Gly Ser Val Phe Ile Gly Arg Leu Ile Glu His Met Gln Glu Tyr
                245                 250                 255

Ala Cys Ser Cys Asp Val Glu Glu Ile Phe Arg Lys Val Arg Phe Ser
            260                 265                 270

Phe Glu Gln Pro Asp Gly Arg Ala Gln Met Pro Thr Thr Glu Arg Val
        275                 280                 285

Thr Leu Thr Arg Cys Phe Tyr Leu Phe Pro Gly His
    290                 295                 300
```

<210> 10
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:fluorogenic substrate

<220>
<223> Asp at position 1 is modified with an acetyl group; Asp at position 4 is modified with an a-(4-methyl-coumaryl-7-amide) group

<400> 10
Asp Glu Val Asp
  1

<210> 11
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: PCR primer

<220>
<223> Tyr at position 1 is modified with an acetyl group; Asp at position 4 may be modified with a CH2OC(O)-[2,6(CF3)2] Ph group or an a-(4-methyl-coumaryl-7-amide) group.

<400> 11
Tyr Val Ala Asp
1

<210> 12
<211> 37
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: PCR primer

<400> 12
gactcgagtc tagagtcgac ttttttttttt ttttttt 37

<210> 13
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: PCR primer

<400> 13
aagtgagcag atcagaattg ag 22

<210> 14
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: PCR primer

<400> 14
gactcgagtc tagagtcgac 20

<210> 15
<211> 31
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: PCR primer

<400> 15
gaggatcccc aaatgcaaac tggatgatga c 31

<210> 16
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: PCR primer

<400> 16
gccaccagct aaaaacattc tcaa 24

<210> 17
<211> 31
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: PCR primer

<400> 17
ttggatccag atggacttca gcagaaatct t 31

<210> 18
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: PCR primer

<400> 18
attctcaaac cctgcatcca agtg 24

<210> 19
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: PCR primer

<400> 19
ggcttctcgt ggttcccaga gc 22

<210> 20
<211> 21
<212> DNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: PCR primer

<400> 20
tgctcttcct gtgtagagat g 21